

REMARKS

By this Amendment, applicant is replacing existing claims 1, 6, 7, 9 and 10 with new claims 1, 6, 7, 9 and 10, above. Attached hereto as Appendix A is a marked-up version showing the changes made to the claims herein. Applicant retains the right to file one or more divisional or continuation patent applications claiming the deleted subject matter.

Applicant by this Amendment has amended the claims of the subject application so that they are restricted to compounds of Group I, which applicant elected without traverse in the Communication filed March 26, 2002. It is noted that the Examiner has maintained that the originally-claimed subject matter falling outside of the scope of Group I is drawn to subject matter that is patentably distinct from the subject matter of Group I.

Applicant asserts that the rejections recited in (1)(a) and (2) of the May 1, 2002 Office Action are rendered moot in light of the restriction herein of the claims to Group I.

Applicant has herein replaced the terms such as "comprises", "contain", "contains" and "containing" recited in claims 1, 6 and 7 with the terms "includes" and the like in order to overcome the rejection recited in (1)(b) of the May 1, 2002 Office Action.

The Examiner has asserted in (1)(c) of the May 1, 2002 Office Action that the term "carbocyclic ring" where used to include heterocyclic ring in the claims is repugnant to the "usual" meaning of the term "carbocyclic ring". In view thereof, applicant has deleted from the claims those recitations of "carbocyclic" which encompassed "heterocyclic".

The Examiner has also asserted in (1)(c) that the term "alkyl" as in "alkyl . . . optionally contain one double or triple bond" in the claims is repugnant to the "usual meaning of the term "alkyl". According to the Examiner, the accepted meaning is "saturated carbon chain" only.

Applicant respectfully traverses this rejection. Applicant maintains that the term "alkyl" can be recognized in the art to refer to hydrocarbon chains comprising one or more unsaturated bonds. As evidence thereof, applicant attaches hereto a copy of page 834 of Organic Chemistry, Third Edition, T. W. Graham Solomons, University of South Florida, John Wiley & Sons, Inc. (1984), an organic chemistry textbook well accepted in the art. Solomons uses the term "alkyl" in "alkylamines", and uses "alkylamines" to refer not only to amines comprising saturated hydrocarbon moieties, such as ethylamine, but also to amines comprising unsaturated groups, such as allylamine. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the rejection recited in

(1)(c) with respect to applicant's use of the term "alkyl".

Applicant has deleted the clause containing the word "preferably" in claims 6 and 7, in response to the Examiner's rejection recited in (1)(c).

Applicant has deleted the clause containing the phrase "including but not limited to" in claims 9 and 10 in view of (1)(d).

The Examiner rejected claim 12-16 and 18-22 under 35 USC 112, first paragraph, in (3). According to the Examiner, the specification provides no guidance for combination therapy. The Examiner stated that formulation of a combined therapy requires undue experimentation and even co-administration requires extensive research because drugs can allegedly interact with each other by inhibiting metabolism and protein binding.

Applicant respectfully traverses this rejection. The specification described formulation and administration methods on pages 30-31. Moreover, the Examiner has provided no concrete reasons or evidence that the compounds recited in applicant's claims would be contra-indicated by any other drug, generally or specifically.

The Examiner rejected claims 1, 6, 7, 9-11 and 17 under the judicially created doctrine of obviousness-type double patenting as allegedly obvious over the claims of US Patent No. 5,962,479 (hereinafter '479). It is noted that the Examiner did not reject claims 2-5, 8, 12-16 and 18-22 as obvious over the claims of '479. Applicant will consider filing a terminal disclaimer upon consideration of otherwise allowable subject matter.

Claim 8 should no longer be objected to, since the claim from which it depends should now be deemed allowable by the Examiner.

It is believed that the amendments herein overcome the Examiner's rejections and objections set forth in the May 1, 2002 Office Action. Applicant hereby requests the earliest possible notification of allowable subject matter.

If a Telephone Interview would be of assistance in advancing the prosecution of this application, the Examiner is kindly to telephone Applicant's undersigned attorney at the telephone provided.

No fee, other than the fee for the three month extension of time authorized in the Petition filed herewith is believe necessary for filing this Amendment. However, if any other fee is found necessary for filing this Amendment, authorization to charge such fee to Deposit Account No. 16-1445 is hereby given.

Respectfully submitted,

Date: November 1, 2002

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University of South Florida

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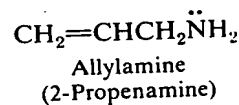
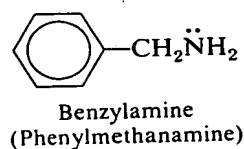
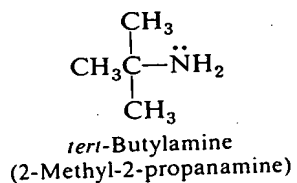
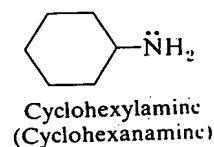
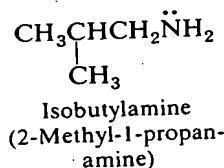
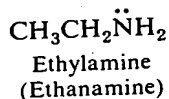
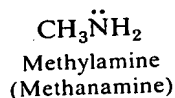
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Amines

19.1 NOMENCLATURE

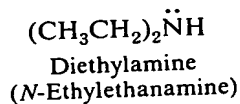
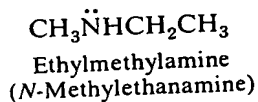
In common nomenclature most primary amines are named as *alkylamines*. In systematic nomenclature (in parentheses below) they are named by adding the suffix *-amine* to the name of the chain or ring system to which the NH_2 group is attached with elision of the final *e*.

Primary Amines



Most secondary and tertiary amines are named in the same general way. In common nomenclature we either designate the organic groups individually if they are different, or use the prefixes *di-* or *tri-* if they are the same. In systematic nomenclature we use the locant *N* to designate substituents attached to nitrogen.

Secondary Amines

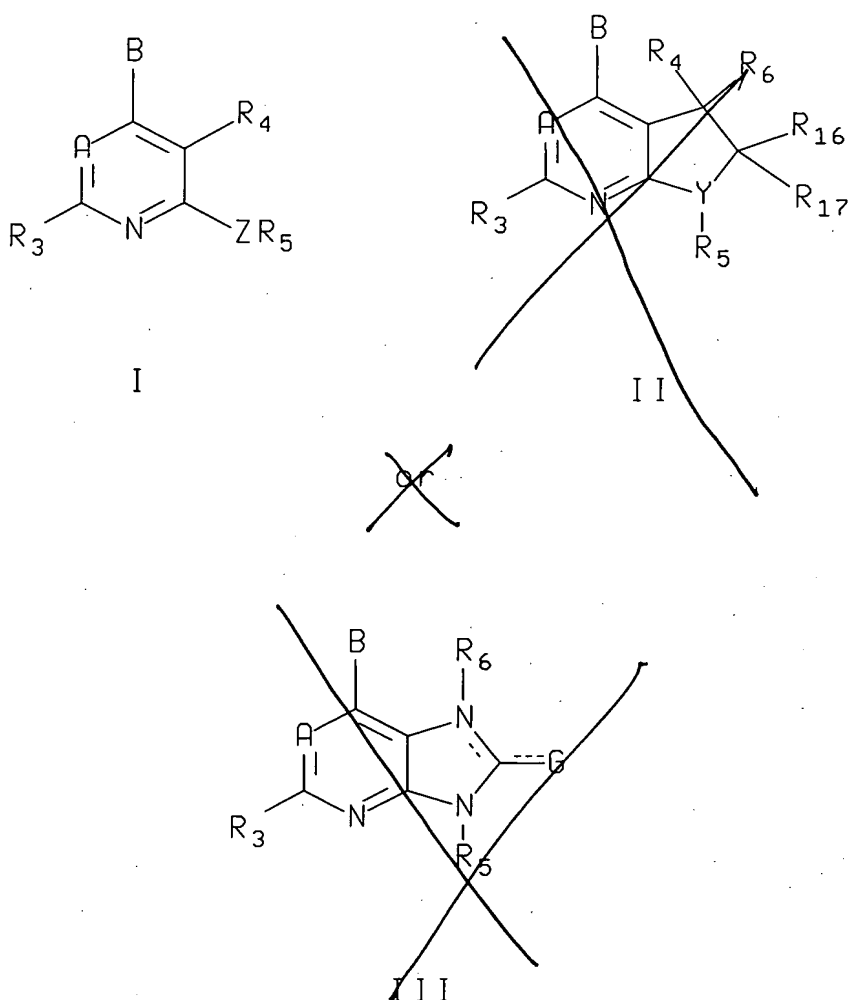


APPENDIX A

Claims 1, 6, 7, 9 and 10 are amended as follows:

VERSION WITH MARKINGS TO SHOW CHANGES MADE – DO NOT ENTER:

1. (Amended) A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

[the dashed lines represent optional double bonds, with the proviso that when the dashed line in C—G represent a double bond, then the dashed line in N(R₆)—C does not represent a double

~~bond; and with the proviso that when the dashed line in $N(R_6)-C$ represents a double bond, R_6 is absent in formula III and the dashed line in $C-G$ does not represent a double bond;~~

A is $-CR_7$ [~~or N~~];

B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_2R_{12})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_1$, $-CHR_1OR_2$, $-CHR_2SR_1$, $-C(S)R_2$, $-C(O)R_2$, $-CHR_2NR_1R_2$, $-CHR_1NHR_2$, $-CHR_1N(CH_3)R_2$, or $-NR_{12}NR_1R_2$;

~~[when the dashed line in $C-G$ represents a double bond, then G is hydrogen, oxygen, sulfur, NH, or $N(C_4-C_4 \text{ alkyl})$;~~

~~when the dashed line in $C-G$ does not represent a double bond, then $C-G$ is $C(H)(NH_2)$, CH_2 , $C(H)(\text{methoxy})$, $C(H)(\text{ethoxy})$, $C(H)(O(C_2-C_4 \text{ alkyl}))$, $C(H)(\text{halo})$, $C(H)(\text{trifluoromethoxy})$, $C(H)(\text{methyl})$, $C(H)(\text{ethyl})$, $C(H)(C_3-C_4 \text{ alkyl})$, $C(H)(S(C_4-C_4 \text{ alkyl}))$, $C(C_4-C_4 \text{ alkyl})(C_4-C_4 \text{ alkyl})$, cyclopropyl, $C(H)(\text{cyclopropyl})$, thiomethoxy, $C(H)(NH_2)$, $C(H)(NHCH_3)$, $C(H)(N(CH_3)_2)$, or $C(H)(\text{trifluoromethyl})$;~~

~~wherein said cyclopropyl, methoxy, ethoxy, C_2-C_4 alkyl, and C_4-C_4 alkyl groups of $C-G$ may optionally be substituted by one OH, methoxy, or trifluoromethoxy, or may optionally be substituted by from one to six fluoro atoms;~~

~~Y is CH or N;~~

Z is NH, O, S, $-N(C_1-C_2 \text{ alkyl})$, $-NC(O)CF_3$, or $-C(R_{13}R_{14})$, wherein R_{13} and R_{14} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{13} and R_{14} is cyano and the other is hydrogen or methyl, or $-C(R_{13}R_{14})$ is a cyclopropyl group, or Z is nitrogen or CH and forms a five or six membered heterocyclic ring fused with R_5 , which ring optionally [~~comprises~~] includes two or three further hetero members selected independently from oxygen, nitrogen, NR_{12} , and $S(O)_m$, and optionally [~~comprises~~] includes from one to three double bonds, and is optionally substituted with halo, C_1-C_4 alkyl, $-O(C_1-C_4 \text{ alkyl})$, NH_2 , $NHCH_3$, $N(CH_3)_2$, CF_3 , or OCF_3 , with the proviso that said ring does not [~~contain~~] include any $-S-S-$, $-S-O-$, $-N-S-$, or $-O-O-$ bonds, and does not [~~comprise~~] include more than two oxygen or $S(O)_m$ heterologous members;

R_1 is $C(O)H$, $C(O)(C_1-C_6 \text{ alkyl})$, $C(O)(C_1-C_6 \text{ alkylene})(C_3-C_8 \text{ cycloalkyl})$, $C(O)(C_3-C_8 \text{ cycloalkylene})(C_3-C_8 \text{ cycloalkyl})$, $C(O)(C_1-C_6 \text{ alkylene})(C_4-C_8 \text{ heterocycloalkyl})$, $-C(O)(C_3-C_8 \text{ cycloalkylene})(C_4-C_8 \text{ heterocycloalkyl})$, $C_1-C_6 \text{ alkyl}$, $C_3-C_8 \text{ cycloalkyl}$, $C_4-C_8 \text{ heterocycloalkyl}$, $-(C_1-C_6 \text{ alkylene})(C_3-C_8 \text{ cycloalkyl})$, $-(C_3-C_8 \text{ cycloalkylene})(C_3-C_8 \text{ cycloalkyl})$, $-(C_1-C_6 \text{ alkylene})(C_4-C_8 \text{ heterocycloalkyl})$, $-(C_3-C_8 \text{ cycloalkylene})(C_4-C_8 \text{ heterocycloalkyl})$, or $-O\text{-aryl}$, or $-O-(C_1-C_6 \text{ alkylene})\text{-aryl}$; wherein said aryl, $C_4-C_8 \text{ heterocycloalkyl}$, $C_1-C_6 \text{ alkyl}$, $C_3-C_8 \text{ cycloalkyl}$, C_3-C_8

cycloalkylene, and C₁-C₅ alkylene groups may each independently be optionally substituted with from one to six fluoro and may each independently be optionally substituted with one or two substituents R₈ independently selected from the group consisting of C₁-C₄ alkyl, -C₃-C₈ cycloalkyl, hydroxy, chloro, bromo, iodo, CF₃, -O-(C₁-C₆ alkyl), -O-(C₃-C₅ cycloalkyl), -O-CO-(C₁-C₄ alkyl), -O-CO-NH(C₁-C₄ alkyl), -O-CO-N(R₂₄)(R₂₅), -N(R₂₄)(R₂₅), -S(C₁-C₄ alkyl), -S(C₃-C₅ cycloalkyl), -N(C₁-C₄alkyl)CO(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), CN, NO₂, -OSO₂(C₁-C₄ alkyl), S⁺(C₁-C₆ alkyl)(C₁-C₂ alkyl)I⁻, -SO(C₁-C₄ alkyl) and -SO₂(C₁-C₄ alkyl); and wherein the C₁-C₆ alkyl, C₁-C₆ alkylene, C₅-C₈ cycloalkyl, C₅-C₈ cycloalkylene, and C₅-C₈ heterocycloalkyl moieties of R₁ may optionally independently [contain] include from one to three double or triple bonds; and wherein the C₁-C₄ alkyl moieties and C₁-C₆ alkyl moieties of R₈ can optionally independently be substituted with hydroxy, amino, C₁-C₄ alkyl, aryl, -CH₂-aryl, C₃-C₅ cycloalkyl, or -O-(C₁-C₄ alkyl), and can optionally independently be substituted with from one to six fluoro, and can optionally [contain] include one or two double or triple bonds; and wherein each heterocycloalkyl group of R₁ [contains] includes from one to three heteromoieties selected from oxygen, S(O)_m, nitrogen, and NR₁₂;

R₂ is hydrogen, C₁-C₁₂ alkyl, C₃-C₈ cycloalkyl, C₄-C₈ heterocycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), aryl, -(C₁-C₆ alkylene)aryl, or -(C₃-C₈ cycloalkylene)(aryl); wherein each of the foregoing R₂ groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and C₁-C₆ alkyl, wherein one of said one to three substituents can further be selected from bromo, iodo, C₁-C₆ alkoxy, -OH, -O-CO-(C₁-C₆ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), S⁺(C₁-C₆ alkyl)(C₁-C₂ alkyl)I⁻, CN, and NO₂; and wherein the C₁-C₁₂ alkyl, -(C₁-C₆ alkylene), -(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene), and -(C₅-C₈ heterocycloalkyl) moieties of R₂ may optionally independently [contain] include from one to three double or triple bonds; and wherein each heterocycloalkyl group of R₂ [contains] includes from one to three heteromoieties selected from oxygen, S(O)_m, nitrogen, and NR₁₂;

or when R₁ and R₂ are as in -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₁R₂ or -NR₁R₂, R₁ and R₂ of B may form a saturated 5- to 8-membered ring which may optionally [contain] include one or two double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen, S(O)_m, nitrogen or NR₁₂; and which [carbocyclic] ring can optionally be substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, C₁-C₄ alkyl, fluoro, chloro,

bromo, iodo, CF_3 , $-\text{O}-(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{O}-\text{CO}-(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{O}-\text{CO}-\text{NH}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{O}-\text{CO}-\text{N}(\text{C}_1-\text{C}_2 \text{ alkyl})(\text{C}_1-\text{C}_2 \text{ alkyl})$, $-\text{NH}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{N}(\text{C}_1-\text{C}_2 \text{ alkyl})(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{S}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{N}(\text{C}_1-\text{C}_4 \text{ alkyl})\text{CO}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{NHCO}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{COO}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{CONH}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{CON}(\text{C}_1-\text{C}_4 \text{ alkyl})(\text{C}_1-\text{C}_2 \text{ alkyl})$, CN , NO_2 , $-\text{OSO}_2(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{SO}(\text{C}_1-\text{C}_4 \text{ alkyl})$, and $-\text{SO}_2(\text{C}_1-\text{C}_4 \text{ alkyl})$, wherein one of said one to three substituents can further be selected from phenyl;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3 , NH_2 , $\text{NH}(\text{C}_1-\text{C}_2 \text{ alkyl})$, $\text{N}(\text{CH}_3)_2$, $-\text{NHCOCF}_3$, $-\text{NHCH}_2\text{CF}_3$, $\text{S}(\text{O})_m(\text{C}_1-\text{C}_4 \text{ alkyl})$, CONH_2 , $-\text{CONHCH}_3$, $\text{CON}(\text{CH}_3)_2$, $-\text{CF}_3$, or CH_2OCH_3 ;

R_4 is hydrogen, C_1-C_4 alkyl, C_3-C_5 cycloalkyl, $-(\text{C}_1-\text{C}_4 \text{ alkylene})(\text{C}_3-\text{C}_5 \text{ cycloalkyl})$, $-(\text{C}_3-\text{C}_5 \text{ cycloalkylene})(\text{C}_3-\text{C}_5 \text{ cycloalkyl})$, cyano, fluoro, chloro, bromo, iodo, $-\text{OR}_{24}$, C_1-C_6 alkoxy, $-\text{O}-(\text{C}_3-\text{C}_5 \text{ cycloalkyl})$, $-\text{O}-(\text{C}_1-\text{C}_4 \text{ alkylene})(\text{C}_3-\text{C}_5 \text{ cycloalkyl})$, $-\text{O}-(\text{C}_3-\text{C}_5 \text{ cycloalkylene})(\text{C}_3-\text{C}_5 \text{ cycloalkyl})$, $-\text{CH}_2\text{SC}(\text{S})\text{O}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{CH}_2\text{OCF}_3$, CF_3 , amino, nitro, $-\text{NR}_{24}\text{R}_{25}$, $-(\text{C}_1-\text{C}_4 \text{ alkylene})-\text{OR}_{24}$, $-(\text{C}_1-\text{C}_4 \text{ alkylene})\text{Cl}$, $-(\text{C}_1-\text{C}_4 \text{ alkylene})\text{NR}_{24}\text{R}_{25}$, $-\text{NHCOR}_{24}$, $-\text{NHCONR}_{24}\text{R}_{25}$, $-\text{C}=\text{NOR}_{24}$, $-\text{NHNR}_{24}\text{R}_{25}$, $-\text{S}(\text{O})_m\text{R}_{24}$, $-\text{C}(\text{O})\text{R}_{24}$, $-\text{OC}(\text{O})\text{R}_{24}$, $-\text{C}(\text{O})\text{Cl}$, $-\text{C}(\text{O})\text{NR}_{24}\text{R}_{25}$, $-\text{C}(\text{O})\text{NHNR}_{24}\text{R}_{25}$, and $-\text{COOR}_{24}$, wherein the alkyl and alkylene groups of R_4 may optionally independently [contain] include one or two double or triple bonds and may optionally independently be substituted with one or two substituents R_{10} independently selected from hydroxy, amino, $-\text{NHCOCH}_3$, $-\text{NHCOCH}_2\text{Cl}$, $-\text{NH}(\text{C}_1-\text{C}_2 \text{ alkyl})$, $-\text{N}(\text{C}_1-\text{C}_2 \text{ alkyl})(\text{C}_1-\text{C}_2 \text{ alkyl})$, $-\text{COO}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{COOH}$, $-\text{CO}(\text{C}_1-\text{C}_4 \text{ alkyl})$, C_1-C_6 alkoxy, C_1-C_3 thioalkyl, cyano and nitro, and with one to four substituents independently selected from fluoro and chloro;

R_5 is aryl or heteroaryl and is substituted with from one to four substituents R_{27} independently selected from halo, C_1-C_{10} alkyl, $-(\text{C}_1-\text{C}_4 \text{ alkylene})(\text{C}_3-\text{C}_8 \text{ cycloalkyl})$, $-(\text{C}_1-\text{C}_4 \text{ alkylene})(\text{C}_4-\text{C}_8 \text{ heterocycloalkyl})$, $-(\text{C}_3-\text{C}_8 \text{ cycloalkyl})$, $-(\text{C}_4-\text{C}_8 \text{ heterocycloalkyl})$, $-(\text{C}_3-\text{C}_8 \text{ cycloalkylene})(\text{C}_3-\text{C}_8 \text{ cycloalkyl})$, $-(\text{C}_3-\text{C}_8 \text{ cycloalkylene})(\text{C}_4-\text{C}_8 \text{ heterocycloalkyl})$, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, nitro, cyano, $-\text{NR}_{24}\text{R}_{25}$, $-\text{NR}_{24}\text{COR}_{25}$, $-\text{NR}_{24}\text{CO}_2\text{R}_{26}$, $-\text{COR}_{24}$, $-\text{OR}_{25}$, $-\text{CONR}_{24}\text{R}_{25}$, $-\text{CO}(\text{NOR}_{22})\text{R}_{23}$, $-\text{CO}_2\text{R}_{26}$, $-\text{C}=\text{N}(\text{OR}_{22})\text{R}_{23}$, and $-\text{S}(\text{O})_m\text{R}_{23}$; wherein said C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, $(\text{C}_1-\text{C}_4 \text{ alkylene})$, $(\text{C}_3-\text{C}_8 \text{ cycloalkyl})$, $(\text{C}_3-\text{C}_8 \text{ cycloalkylene})$, and $(\text{C}_4-\text{C}_8 \text{ heterocycloalkyl})$ groups can be optionally substituted with from one to three substituents independently selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, $(\text{C}_1-\text{C}_4 \text{ alkylene})(\text{C}_3-\text{C}_8 \text{ cycloalkyl})$, $-(\text{C}_3-\text{C}_8 \text{ cycloalkylene})(\text{C}_3-\text{C}_8 \text{ cycloalkyl})$, C_1-C_4 haloalkyl, hydroxy, C_1-C_6 alkoxy, nitro halo, cyano, $-\text{NR}_{24}\text{R}_{25}$, $-\text{NR}_{24}\text{COR}_{25}$, $\text{NR}_{24}\text{CO}_2\text{R}_{26}$, $-\text{COR}_{24}$, $-\text{OR}_{25}$, $-\text{CONR}_{24}\text{R}_{25}$, CO_2R_{26} , $-\text{CO}(\text{NOR}_{22})\text{R}_{23}$, and $-\text{S}(\text{O})_m\text{R}_{23}$; and wherein two adjacent substituents of the R_5 group can optionally form a 5-7

membered ring, saturated or unsaturated, fused to R⁵, which ring optionally can [contain] include one, two, or three heterologous members independently selected from O, S(O)_m, and N, but not any -S-S-, -O-O-, -S-O-, or -N-S- bonds, and which ring is optionally substituted with C₁-C₄ alkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C₁-C₄ haloalkyl, nitro, halo, cyano -NR₂₄R₂₅, NR₂₄COR₂₅, NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, CO₂R₂₆, -CO(NOR₂₆)R₂₅, or -S(O)_mR₂₃; wherein one of said one to four optional substituents R₂₇ can further be selected from -SO₂NH(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -SO₂NH(C₃-C₈ cycloalkyl), -SO₂NH(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SO₂NH₂, -NHSC₂(C₁-C₄ alkyl), -NHSC₂(C₃-C₈ cycloalkyl), -NHSC₂(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), and -NHSC₂(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl); and wherein the alkyl, and alkylene groups of R₅ may independently optionally [contain] include one double or triple bond;

R₆ is hydrogen, C₁-C₃ alkyl, C₃-C₈ cycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), or -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), wherein said alkyl and cycloalkyl may optionally be substituted with one hydroxy, methoxy, ethoxy or fluoro group;

[or, wherein the compound is a compound of formula II, R₆ and R₄ can together form an oxo (=O) group, or can be connected to form a 3-8 membered carbocyclic ring, optionally containing one to three double bonds, and optionally containing one, two, or three heterologous ring members selected from O, SO_m, N, and NR₁₂, but not containing any -O-O-, -S-O-, -S-S-, or -N-S- bonds, and further optionally substituted with C₁-C₄ alkyl or C₃-C₆ cycloalkyl, wherein said C₁-C₄ alkyl substituent may optionally contain one double or triple bond;]

R₇ is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C₁-C₂ alkyl), -O(cyclopropyl), -COO(C₁-C₂ alkyl), -CCC(C₃-C₈ cycloalkyl), -OCF₃, CF₃, -CH₂OH, or CH₂OCH₃;

R₁₁ is hydrogen, hydroxy, fluoro, ethoxy, or methoxy;

R₁₂ is hydrogen or C₁-C₄ alkyl;

~~[R₁₆ and R₁₇ are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy, except that R₁₆ and R₁₇ are not both methoxy or ethoxy;~~

~~or R₁₆ and R₁₇ together form an oxo (=O) group;~~

~~or R₁₆ and R₁₇ are connected to form a 3-8 membered carbocyclic ring, optionally containing one to three double bonds, and optionally containing from one to three heterologous ring members selected from O, SO_m, N, and NR₁₂, but not containing any -O-O-, -S-O-, -S-S-, or -N-S-~~

bonds, and further optionally substituted with C₁-C₄ alkyl or C₃-C₈ cycloalkyl, wherein said C₁-C₄ alkyl substituent may optionally contain one double or triple bond;

R₂₂ is independently at each occurrence selected from hydrogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₃-C₈ alkenyl, C₃-C₈ alkynyl, C₃-C₈ cycloalkyl, (C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), and (C₁-C₄ alkylene)(C₃-C₈ cycloalkyl);

R₂₃ is independently at each occurrence selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₅ alkoxyalkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), aryl, -(C₁-C₄ alkylene)aryl, piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, and thiomorpholine;

R₂₄ and R₂₅ are independently at each occurrence selected from hydrogen, -C₁-C₄ alkyl, C₁-C₄ haloalkyl, especially CF₃, -CHF₂, CF₂CF₃, or CH₂CF₃, -(C₁-C₄ alkylene)OH, -(C₁-C₄ alkylene)-O-(C₁-C₄ alkyl), -(C₁-C₄ alkylene)-O-(C₃-C₈ cycloalkyl), C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -C₄-C₈ heterocycloalkyl, -(C₁-C₄ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), aryl, and -(C₁-C₄ alkylene)(aryl), wherein the -C₄-C₈ heterocycloalkyl groups can each independently optionally be substituted with aryl, CH₂-aryl, or C₁-C₄ alkyl, and can optionally [contain] include one or two double or triple bonds; or, when R₂₄ and R₂₅ are as NR₂₄R₂₅, -C(O)NR₂₄R₂₅, -(C₁-C₄ alkylene)NR₂₄R₂₅, or -NHCONR₂₄R₂₅, then NR₂₄R₂₅ may further optionally form a 4 to 8 membered heterocyclic ring optionally [containing] including one or two further hetero members independently selected from S(O)_m, oxygen, nitrogen, and NR₁₂, and optionally [containing] including from one to three double bonds;

R₂₆ is independently at each occurrence selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), aryl, and -(C₁-C₄ alkylene)(aryl); and

wherein each m is independently zero, one, or two,

with the proviso that heterocycloalkyl groups of the compound of formula I, II, or III do not [comprise] include any -S-S-, -S-O-, -N-S-, or -O-O- bonds, and do not [comprise] include more than two oxygen or S(O)_m heterologous members.

6. (Amended) A compound of formula I according to claim 1, wherein Z is O; B is -NHCHR₁R₂, wherein R₁ is -C(O)H, -C(O)(C₁-C₆ alkyl), or -C₁-C₆ alkyl, wherein said C₁-C₆ alkyl is optionally substituted with from one to six fluoro atoms or one or two R₈ independently selected from -C₁-C₄ alkyl, hydroxy and -O-(C₁-C₆ alkyl), and wherein R₂ is -C₁-C₁₂ alkyl

optionally ~~[containing]~~ including from one to three double or triple bonds and optionally substituted with from one three substituents selected from fluoro and C₁-C₆ alkyl; R₅ is phenyl, pyridyl or pyrimidyl, substituted with two or three R₂₇ groups selected from halo, -(C₁-C₄ haloalkyl), -C(O)R₂₄, -OR₂₅, -C(O)NR₂₄R₂₅, and C₁-C₁₀ alkyl which is optionally substituted with one to three substituents~~[-preferably one substituent,]~~ selected from hydroxy, C₁-C₆ alkoxy, and -NR₂₄R₂₅; and R₄ is -C(O)NR₂₄R₂₅.

7. (Amended) A compound of formula I according to claim 1, wherein Z is O; B is -NHCHR₁R₂, wherein R₁ of -NHCHR₁R₂ is -C(O)H, -C(O)(C₁-C₆ alkyl), or -C₁-C₆ alkyl, wherein said C₁-C₆ alkyl is optionally substituted with from one to six fluoro atoms or one or two R₈ independently selected from -C₁-C₄ alkyl, hydroxy and -O-(C₁-C₆ alkyl), and wherein R₂ of -NHCHR₁R₂ is -C₁-C₁₂ alkyl optionally ~~[containing]~~ including from one to three double or triple bonds and optionally substituted with from one three substituents selected from fluoro and C₁-C₆ alkyl; R₅ is phenyl, pyridyl or pyrimidyl, substituted with two or three R₂₇ groups selected from halo, -(C₁-C₄ haloalkyl), -C(O)R₂₄, -OR₂₅, -C(O)NR₂₄R₂₅, and C₁-C₁₀ alkyl which is optionally substituted with one to three substituents~~[-preferably one substituent,]~~ selected from hydroxy, C₁-C₆ alkoxy, and -NR₂₄R₂₅; and R₄ is -NR₁R₂, wherein R₁ of -NR₁R₂ is C₁-C₆ alkyl, C₃-C₈ cycloalkyl, or -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), and R₂ of -NR₁R₂ is C₁-C₁₂ alkyl optionally ~~[containing]~~ including from one to three double or triple bonds and optionally substituted with from one three fluoro atoms.

9. A pharmaceutical composition for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF~~[-including but not limited to disorders induced or facilitated by CRF]~~, or (b) a disorder or condition selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, and specific phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease;

gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies or addictions, including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; infertility; head trauma, spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human-animal interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and Syndrome X in a mammal or bird, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder or condition, and a pharmaceutically acceptable carrier.

10. A method for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF[~~including but not limited to disorders induced or facilitated by CRF~~], or (b) a disorder or condition selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, and specific phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer, diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies or addictions, including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; infertility; head trauma; spinal cord trauma; ischemic neuronal damage,

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including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human-animal interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and Syndrome X in a mammal or bird, comprising administering to a subject in need of said treatment an amount of a compound according to claim 1, that is effective in treating such disorder or condition.